The 4th International Symposium on APS Type 1

September 18, 2021, 12 - 4 pm EDT

Rapporteur's Report

Si Yue Guo, PhD

Table of Contents

List of Abbreviations 2

Introduction 3

Plenary Sessions 4

Autoantibodies against type I IFNs in patients with APS-1 4

Clinical management of COVID-19 and vaccination responses to SARS-CoV-2 in APS-1/APECED patients 6

Discovery of novel, clinically correlated autoantibodies in APS-1 by high-throughput PhIP-Seq 8

AIRE & Cancer 9

Breakout Group Sessions 11

Newly diagnosed patients of APS Type 1 11

Managing Calcium and Adrenal Insufficiency 12

Clinicians and Scientists Meet and Greet 13

Children and Youth Meet and Greet 14

Appendix 15

Agenda 15

Biography of Speakers 16

References 18

List of Abbreviations

Ab	Antibody
AIRE	Autoimmune regulator
Anti-S	Anti-spike (protein)
APECED	Autoimmune polyendocrinopathy candidiasis ecto-dermal dystrophy
APS-1	Autoimmune Polyglandular Syndrome Type 1
Auto-Ab	Autoantibody
CLIA	Clinical Laboratory Improvement Amendments
COVID-19	Coronavirus disease 2019
CT	Computerized tomography
IFN	Interferon
mAb	Monoclonal antibody
PhIP-Seq	Phage immunoprecipitation sequencing
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Introduction

The APS Type 1 Foundation Inc. exists to drive research to improve the lives of people with Autoimmune Polyglandular Syndrome Type 1 (APS-1 or APS Type 1), a rare genetic disorder caused by mutations of the autoimmune regulator (AIRE) gene. APS-1 is also sometimes referred to as autoimmune polyendocrinopathy candidiasis ectodermal dystrophy or APECED. The foundation helps with education, awareness and fundraising for critical research in APS-1. The ultimate goal is to find a cure for this disease.

Since 2015, the APS Type 1 Foundation has supported a biennial symposium on this rare disease. The symposia unite patients, families, clinicians, and scientists worldwide to exchange the latest developments in research and management of APS Type 1.

The *4th International Symposium on APS Type 1* took place on September 18, 2021, with over 150 participants, including patients, families, caregivers, researchers, and clinicians, attending virtually due to the COVID-19 pandemic. During the plenary sessions, participants learned about recent research, notably the role of autoantibodies in APS-1 and the effect of COVID-19 and SARS-CoV-2 vaccines on APS-1 patients, and the relationship between AIRE and cancer. The scientific presentations were followed by breakout group discussions for patients and families to share experiences and resources and for scientists and clinicians to brainstorm a strategic research agenda.

The APS Type 1 Foundation gratefully acknowledges support from SickKids Hospital & Julia's Fund at the SickKids Foundation. The *5th International Symposium on APS Type 1* will be held in Toronto, Canada in 2023. To learn more and to watch video recordings of the symposia, please visit www.apstype1.org/education/symposium/.

Plenary Sessions

Autoantibodies against type I IFNs in patients with APS-1

Paul Bastard (Necker Hospital and Rockefeller University)

Dr. Bastard presented research conducted over the past two years on patients with life-threatening coronavirus disease 19 (COVID-19) and then discussed the disease's risks for patients with APS-1. His work investigated the role of autoantibodies (auto-Abs), antibodies that mistakenly attack the body's own cells and tissues, against interferons (IFN), proteins made by the body in response to the presence of viruses to inhibit their replication. Of the three major types of IFNs, type I is the most important in the fight against viruses and the focus of the work. The results have important implications for patients with APS-1 since almost all of them produce auto-Abs against type I IFNs, generally against the IFN-α and IFN-ω subtypes.[1]

In the general population, there is vast clinical variability in individuals infected with SARS-CoV-2, ranging from an asymptomatic course to rapid death that is often precipitated by lethal pneumonia. While risk factors for severe COVID-19 were identified – primarily age (doubling of risk every five years), sex (higher risk for men), and several other comorbidities such as obesity (moderate risk) – they do not explain why patients within any given epidemiological group have such different responses to infection.

To explain the intervariability of patient responses to SARS-CoV-2, Dr. Bastard and his colleagues examined genetic and autoimmune factors.[2,3] They found that neutralizing autoantibodies against type I IFNs lead to a high risk of severe COVID-19 infection, underlying >15% of critical cases and >20% of cases in people aged 80 and above (see Figure 1). Notably, men were 94% of the patients with auto-Abs in the study.

In the uninfected general population, the prevalence of preexisting neutralizing auto-Abs against type I IFNs increases with age after approximately 65-70 years old, which might explain why age is an important risk factor for severe COVID-19.[4] The early diagnosis and screening of these auto-Abs (ELISA test) provide a means to identify individuals at risk of developing severe COVID-19 and can help with prevention and treatment (IFN-β, mAbs, Ab depletion).

Because APS-1 patients have pre-existing auto-Abs to type I IFNs, they are at risk of severe COVID-19.[5] However, penetrance is incomplete, ranging from asymptomatic COVID-19 to severe pneumonia, according to two studies involving a total of 26 APS-1 patients.[5,6] The risk of developing severe disease can be reduced with vaccination and specific treatments, which will be the focus of the next presentation.

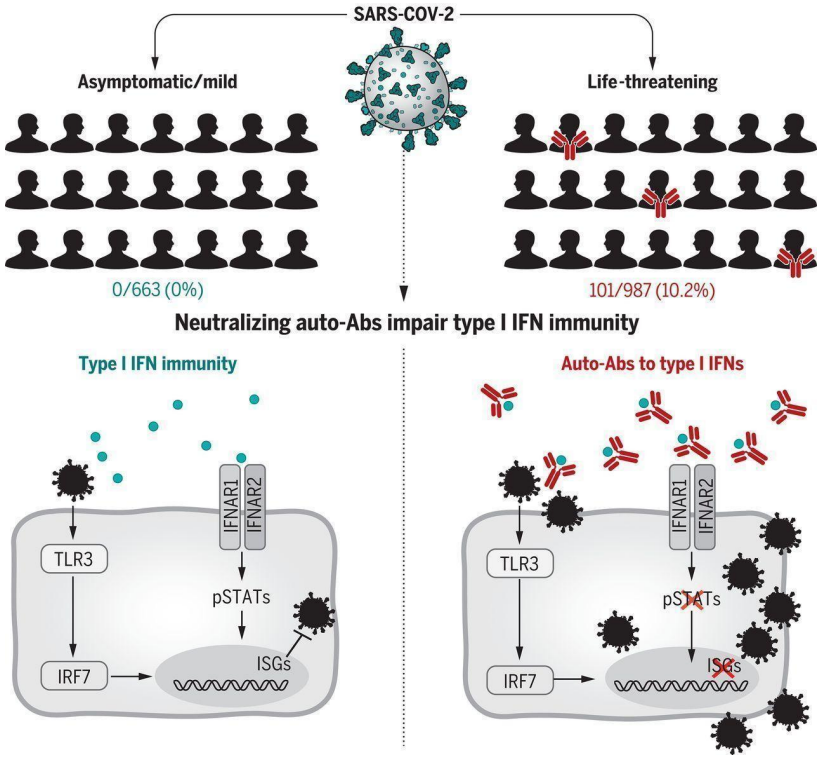


Figure 1 - Neutralizing auto-Abs (in red) to type I IFNs (in blue) underlie life-threatening COVID-19 pneumonia, by impairing the binding of type I IFNs to their receptor and the activation of the downstream responsive pathway. Figure and caption from Ref. [2], Bastard *et al., Science* **370**, 423 (2020).

Auto-abs can underlie other viral infections in APS-1 patients, such as the herpes virus,[7] and cause adverse reaction to the yellow fever live attenuated vaccine[8]. For this reason, Dr. Bastard recommends that APS-1 patients avoid live attenuated vaccines, opting for, e.g. an mRNA vaccine instead.

Overall, the studies that Dr. Bastard highlighted show that type I IFNs are essential for protective immunity against SARS-CoV-2. In both APS-1 patients and the general population,

neutralizing auto-Abs against type I IFNs can be found early and allow for specific treatment and more effective management of COVID-19.

Future research on the neutralizing autoantibodies against type I IFNs aims to explain why they arise in the general population, whether they can cause other viral infections, and how to prevent them without affecting the rest of the immune system.

Prof. Jennifer Orange

Dr. Paul Bastard

Clinical management of COVID-19 and vaccination responses to SARS-CoV-2 in APS-1/APECED patients

Dr. Michail Lionakis (National Institutes of Health)

Dr. Michail Lionakis presented an overview of the clinical course of COVID-19 in APS-1 patients, its management, the tolerability of SARS-CoV-2 vaccination in APS-1 patients, and humoral responses to the vaccination, based on recent literature and case studies.

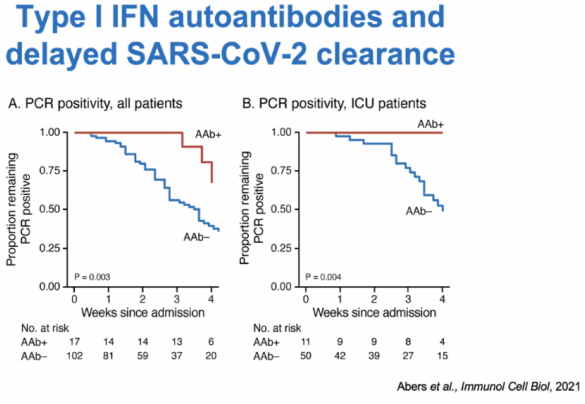
On the clinical course of COVID-19, Dr. Lionakis first reviewed the results of Bastard et al., which reported high rates of severe COVID-19 in APS-1 patients[5]. Up to 40% of COVID-19 patients with APS-1 developed pneumonitis and respiratory failure caused by excess inflammation was a significant cause of death.[9] (In patients without APS-1, those with Type 1 interferon autoantibodies (IFN Auto-Abs) were found to have delayed SARS-CoV-2 clearance.[10])

While patients with APS-1 are at a greater risk of severe COVID-19 due to the higher baseline inflammation and strong immune response, the progression of pneumonitis varied significantly[9] and not all APS-1 patients developed severe COVID-19.[6] Age, absence of pneumonitis, lack of

severe autoimmune manifestation are possible factors, although it is hard to predict on an individual level. A chest CT is recommended for all APS-1 patients with COVID-19.

Dr. Lionakis then presented three case studies to discuss the management of COVID-19 in APS-1, depending on whether the patient is in an early ambulatory phase or a late hypoxemic (low blood oxygen) phase. For late-stage COVID-19, it is critical to treat hypoxemic patients with steroids early. In APS-1 patients, administration of steroids within 24 hours of the onset of hypoxemia, followed by a slow taper over 2-4 weeks, led to great chances of a successful recovery. For high-risk patients in the early stages of COVID-19, early interventions were found to accelerate[1] viral clearance and decrease hospitalization and progression to severe illness and death. Treatment with interferon-beta (IFN-β) or a cocktail of monoclonal antibodies targeting the spike protein (anti-S mAbs) is recommended, although the former is often in short supply.

The recommended course of action for APS-1 patients in the event of COVID-19 depends on the safety of the treatments and the possibility of interfering with the body's natural immune response to the virus. Preliminary results (as of September 2021) suggest that monoclonal antibodies are safe and do not inhibit natural immune response, and it is recommended as an early treatment if IFN-β is not accessible.



Dr. Michail S. Lionakis

Regarding vaccinations, the SARS-CoV-2 vaccines appear to be safe and effective with no unusual toxicities and no new autoimmune manifestations in the interval after vaccination. As well, there was no worsening of preexisting autoimmune manifestations after the vaccine.

[1] Participants with multiple risk factors were considered in these studies, including, but not limited to, those with compromised immune systems.[11,12] A randomized trial of this scale would not be possible in APS-1 patients due to the rarity of the disease.

Humoral responses (an aspect of immunity mediated by macromolecules found in extracellular fluids) to SARS-CoV-2 vaccination are suboptimal in a subset of APS-1 patients. Thus, the NIH recommends booster shots for APS-1 patients.

It remains unclear what to do with patients who do not respond to booster doses of the mRNA vaccines. Some suggestions are to switch to a non-mRNA vaccine such as by Johnson & Johnson or administer anti-spike monoclonal antibodies (Anti-S mAb) as prophylaxis. Regardless, all household members living with an APS-1 patient are advised to be vaccinated and follow public health measures to minimize exposure to SARS-CoV-2.

Discovery of novel, clinically correlated autoantibodies in APS-1 by high-throughput PhIP-Seq

Sara Vazquez (University of California, San Francisco)

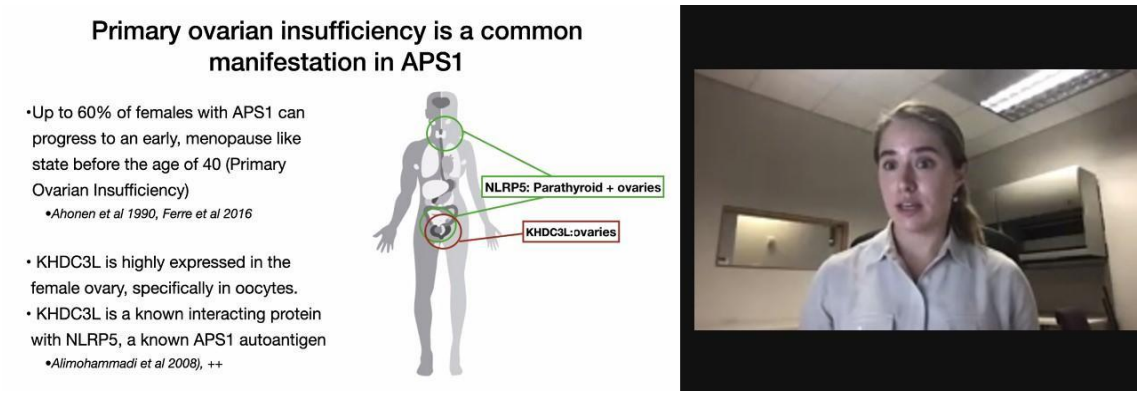
A critical part of our adaptive immune system, antibodies identify and neutralize foreign pathogens, bacteria and viruses in the body. Autoantibodies are antibodies produced by the immune system to target its own cells and organs, which leads to various autoimmune diseases including APS-1. The study of the autoantigens, proteins and tissues targeted by the autoantibodies, enables an improved understanding of autoimmune disease mechanisms and can inform future diagnostics (useful disease biomarkers) and treatments (immunotherapy).[13]

APS-1 patients can develop multiple autoimmune manifestations throughout their life,[14] many of which are still not well understood. In some manifestations, specific autoantibodies correlate with disease,[15,16] so it is important to investigate what the immune system is targeting, in hopes of diagnostic or predictive testing.

Sara Vazquez *et al.* performed proteome-wide programmable phage-display (PhIP-Seq) on samples from APS-1 patients and discovered multiple common antibody targets. Seven novel autoantigens were discovered and clinical phenotyping revealed novel associations between autoantibodies and certain autoimmune diseases. Vazquez elaborated on the disease associations with three common APS-1 manifestations:

- Anti-RFX6 antibodies are associated with intestinal dysfunction, notably the diarrheal subtype that affects motility, digestion, appetite and metabolism.
- Anti-KHDC3L antibodies, expressed in oocytes and the ovary, are associated with primary ovarian insufficiency (POI), which leads to up to 60% of females with APS-1 experiencing an early, menopause-like state by age 40.
- Anti-ACP4 antibodies may be associated with dental enamel hypoplasia.

Ongoing work includes applying PhIP-Seq to larger cohorts of APS-1 patients and investigating other rare immune diseases that might provide insight into APS-1.



Sara Vasquez

AIRE & Cancer

Dr. Maureen Su (University of California, Los Angeles)

APS-1 is caused by mutations in the autoimmune regulator (AIRE) gene. Since the immune system protects against cancer, and weakened immune systems predispose an individual to cancer, is it germane to investigate the relationship between immune dysfunction and cancer.

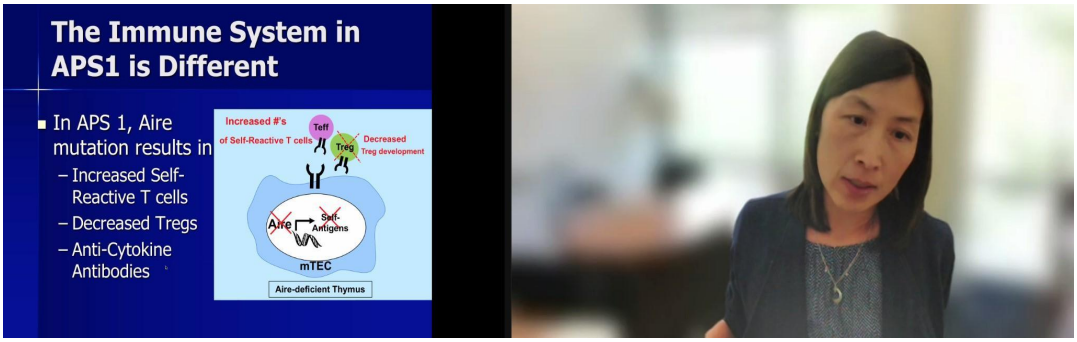
Dr. Maureen Su began by reviewing the role of the immune system in cancer. The 2018 Nobel Prize in Physiology was awarded to James Allision and Tasuku Honjo for their discovery of cancer therapy by activation of the immune system.[17,18] Their treatment strategy was found to be very effective for several types of cancer, including lung cancer, renal cancer, lymphoma and melanoma.

Dr. Su presented studies on two skin conditions, vitiligo and melanoma, showing that autoimmunity and anti-cancer immunity are linked: antibodies that activate immunity improve survival in advanced melanoma.[19]

What does this mean for APS-1? In APS-1, some aspects of the immune system are activated and others are dampened. Given the commonalities between autoimmune vitiligo and melanoma – similar immune cells involved and shared antigens[20] – and that vitiligo is associated with APS-1,[21] can the autoimmune response in AIRE deficiency also fight off melanoma?

Studies in mice report that AIRE deficiency protects against cancer,[21,22] but these studies also observed inflammation and candidiasis, which is linked to cancer.[23] Chronic inflammation can promote cancer development.[24]

Lastly, since APS-1 patients have reported cases of oral, esophageal, and gastrointestinal cancers,[25,26] Dr. Su recommends that patients increase their awareness of oral cancer and conduct routine surveillance for abnormal growths in the mouth, working with their dentists. APS-1 patients should also avoid smoking and treat candidiasis aggressively if infected.



Dr. Maureen Su

Breakout Group Sessions

Newly diagnosed patients of APS Type 1

Chaired by Todd Talarico (APS Type 1 Foundation)

The session aimed to welcome and introduce newly diagnosed patients and their families to the APS Type 1 Foundation. Participants were presented with an overview of the foundation's resources, available at www.apstype1.org. They include:

- Educational videos for patients, families and extended family, including on preparations for and responses to an adrenal crisis,
- Video recordings of expert presentations from past symposia,
- Patient registry and natural history study,
- Networking opportunities for patients and families,
- Access to foundation-funded research, and
- Donations and fundraising opportunities to help support the foundation's work.

Patients were reminded that each individual's situation is unique and that APS-1 manifestations are managed one at a time. Despite that uniqueness, there is a community of families that have walked the road ahead ready to share their experiences and provide support for newly diagnosed patients and one another.

The group also discussed what newly diagnosed patients can expect during their week-long visit at the National Institutes of Health (NIH), which takes a cross-functional approach to their research on APS-1. Patients will be seen by multiple specialists and undergo various tests.

Another topic of discussion was the long-term outlook for patients, specifically the transition from pediatrics to primary care for adult APS-1 patients.

Managing Calcium and Adrenal Insufficiency

Chaired by Dr. Cheri Deal (Université de Montréal and Centre hospitalier universitaire Ste-Justine)

Dr. Cheri Deal spoke to patients and their families and caretakers on the prevention, recognition, treatment, and management of calcium and adrenal insufficiency in APS-1 patients.

It was an interactive discussion where patients and caregivers had an opportunity to ask general questions and share experiences with each other. Dr. Deal shared her experiences treating patients for many years and expressed a commitment to reducing the time to diagnosis.

An adrenal crisis can be avoided with hydrocortisone, fludrocortisone, and salt. APS-1 patients can reduce the risk of upset stomachs through proper hygiene and caution with water and food, especially during foreign travel.

Families and caretakers of young APS-1 patients should learn to recognize symptoms of adrenal crisis in children, such as anoxia, nausea, vomiting, abdominal pain, diarrhea, dizziness, and limb and back pain.

Dr. Deal discussed the treatment of an adrenal crisis in a child by oral ingestion of hydrocortisone (Cortef) while monitoring the child's temperature and other symptoms. Alternatives to hydrocortisone are prednisone and dexamethasone, although the latter is used as a last resort.

Certain measures can be taken in case of emergency outside of the home. Patients should carry with them at all times an emergency card with contact information and clear identification of the adrenal insufficiency (using a wrist band, bracelet, necklace, locket, or even tattoo). Health records must also be kept up to date, e.g. with the help of mobile applications, as well as the contact information for the doctors.

Hospitalizations for acute adrenal insufficiency and hypocalcemic crisis can be avoided by following certain precautions: adhering to the medication schedule and maintaining a daily diet of calcium (e.g. yogurt, milk, tofu) and salt, avoiding gastroenteritis, educating close friends and partners, and always having hydrocortisone available.

Lastly, it is important to keep up with SARS-CoV-2 vaccinations and boosters since APS-1 patients are considered at risk for complications of the virus.

Clinicians and Scientists Meet and Greet

Chaired by Prof. Jennifer Orange (APS Type 1 Foundation)

The discussion between clinicians and scientists and the foundation aimed to identify strategies for greater collaboration and synergy in research across different institutions, as well as how the foundation can support research and meetings. The major themes and objectives that emerged were:

- Improving communication within the research community through frequent meetings (e.g. biannual). In the interim, the community can exchange regular updates using tools such as Slack and Whatsapp.
- Advocating to get CLIA (Clinical Laboratory Improvement Amendments) approval for COVID-19 tests for APS-1 patients. Also, consider testing patients with severe COVID-19 illness to see if they have any auto-immune disease such as APS-1.
- Increasing awareness of the disease, not just among endocrinologists but also dermatologists, other physicians, and dentists, to improve the ability of professionals to diagnose the disease sooner.
- Growing of the network of doctors and patients. This involves reaching out to doctors in more countries, especially in the Global South, and training them to identify the disease. Then, this network can be used to disseminate research and information to doctors and patients more widely.

During the discussion, all participants stressed the importance of involving patients in the meetings and in the research projects, for researchers and doctors to learn about their experiences and to provide up-to-date guidance to patients and their families.

Children and Youth Meet and Greet

Chaired by Gavin Ross (Child Life Specialist at SickKids)

The session was an opportunity for young patients to meet each other and share their experiences and advice. Participants shared stories of their diagnosis, learning about the condition, and how to deal with the rarity of the disease. For instance, there were challenges at school, notably being openly disabled in a school that lacked experience with disabled students; this created an opportunity to help educate the school and create a legacy for future students with disabilities. The young patients were reminded that the patient-doctor relationship is a two-way relationship, with doctors learning extensively about the disease from patients. More recently diagnosed children were reminded of the importance of maintaining a balance between treatment, school, friends, and fun, of asking for help when the situation has become difficult, and of being an advocate for oneself.

Appendix

Agenda

Each presentation will be 30 mins, followed by 15 mins Q&A

12:00-12:05 Introductions (Prof. Jennifer Orange, The APS Type 1 Foundation & Dr. Irene Lara-Corrales, SickKids)

12:05-12:50 Paul Bastard (Necker Hospital and Rockefeller University), Autoantibodies against type I IFNs in patients with APS-1

12:50-1:35 Dr. Michail Lionakis (NIH), Clinical management of COVID-19 and vaccination responses to SARS-CoV-2 in APS-1/APECED patients

1:35-1:45 Health Break

1:45-2:30 Sara Vazquez (UCSF), Discovery of novel, clinically correlated autoantibodies in APS-1 by high-throughput PhIP-Seq

2:30-3:25 Dr. Maureen Su (UCLA), AIRE & Cancer

3:25-3:30 Plenary Session Closing & Thank-Yous by Prof. Jennifer Orange

3:35-4:00 Breakout Group Sessions

- BoG1: Newly diagnosed patients of APS Type 1 (Chaired by Todd Talarico, APS Type 1 Foundation)
- BoG2: Managing Calcium and Adrenal Insufficiency (Chaired by Dr. Cheri Deal - Université de Montréal and CHU Ste-Justine)
- BoG3: Clinicians/Scientists Meet and Greet (Chaired by Prof. Jennifer Orange, APS Type 1 Foundation)
- BoG4: Children/Youth Meet and Greet (Chaired by Gavin Ross, Child Life Specialist at SickKids)

Biography of Speakers

Dr. Paul Bastard is an MD-PhD student in pediatrics and immunology, focusing on the genetic and immunological predisposition to severe viral diseases. Dr. Bastard works at the Necker Hospital in Paris and the laboratory of Human genetics of infectious diseases, headed by Jean-Laurent Casanova.

Dr. Irene Lara-Corrales is an Associate Professor of Paediatrics at the University of Toronto and a Staff Physician in Paediatric Dermatology at The Hospital for Sick Children (SickKids) in Toronto, Canada. She completed her medical training and pediatric residency at the University of Costa Rica, in San Jose, Costa Rica, and her pediatric dermatology training at SickKids. She obtained a Master of Science degree from the University of Toronto. She is involved in numerous clinical and research endeavours, as well as in teaching commitments. She co-directs the Genodermatoses, Epidermolysis Bullosa, Vascular Tumors and Café-au-Lait Screening clinics at SickKids. She is also the co-chair of the hospital's Wound Care Committee. Her research interests include genodermatoses, inflammatory diseases, vascular anomalies and dermatologic problems in hematology/oncology patients.

Dr. Michail S. Lionakis, M.D., Sc.D., Chief, Fungal Pathogenesis Section, Laboratory of Clinical Immunology and Microbiology, NIAID, NIH, obtained his MD and ScD from the University of Crete, Greece. He did clinical and research training at MD Anderson Cancer Center, Baylor College of Medicine, and the NIH. His IRB-approved APS Type-1/APECED clinical research protocol aims to understand the mechanisms of autoimmunity and fungal susceptibility and improve diagnostic and therapeutic strategies for patients.

Prof. Jennifer Orange is the Vice-President of the APS Type 1 Foundation and the mother of an amazing young woman with APS Type 1. Together with Dr. Irene Lara-Corrales, Jennifer founded the 1st International Symposium on APS Type 1 at SickKids Hospital in 2015. She is an Assistant Professor at the Lincoln Alexander School of Law in Toronto, Canada, and a member of the Canadian Human Rights Tribunal. Jennifer has sat on the boards of a number of organizations that work to ensure that patients views are included in their care.

Dr. Maureen A. Su, is a Professor of Microbiology/Immunology and Medical Genetics and Pediatric Endocrinology at the University of California, Los Angeles. She received her bachelor's, master's and medical degrees from Harvard. She completed her pediatrics residency and fellowship in endocrinology at the University of California, San Francisco. Dr. Su seeks to understand what causes autoimmune diseases in order to develop therapeutics to prevent and treat the underlying immune condition. Her work focuses on APS-1, Guillain-Barré Syndrome (GBS), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), and type 1 diabetes.

Sara Vazquez is an MD-PhD student in the labs of Mark Anderson and Joe Derisi at the University of California, San Francisco. She has worked to improve PhIP-seq protocols to enable scalable autoantibody discovery in a wide variety of disease contexts, including APS-1, sporadic autoimmune diabetes, and COVID-19-related autoimmunity. Prior to medical school, Sara worked in Tom Serwold's lab at the Joslin Diabetes Center optimizing hematopoietic stem cell isolation in autoimmune-prone mouse strains. She received her undergraduate degree in Stem Cell and Developmental Biology at Harvard College. Her long-term goal is to combine molecular autoantigen discovery with therapeutic approaches for re-establishing immune tolerance in autoimmunity.

References

1. Meager, A. *et al.* Anti-interferon autoantibodies in autoimmune polyendocrinopathy syndrome type 1. *PLoS Med.* **3**, e289 (2006).

2. Bastard, P. *et al.* Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* **370**, (2020).

3. Zhang, Q. *et al.* Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science* **370**, (2020).

4. Bastard, P. *et al.* Autoantibodies neutralizing type I IFNs are present in 4% of uninfected individuals over 70 years old and account for 20% of COVID-19 deaths. *Sci Immunol* **6**, (2021).

5. Bastard, P. *et al.* Preexisting autoantibodies to type I IFNs underlie critical COVID-19 pneumonia in patients with APS-1. *J. Exp. Med.* **218**, (2021).

6. Meisel, C. *et al.* Mild COVID-19 despite autoantibodies against type I IFNs in autoimmune polyendocrine syndrome type 1. *J. Clin. Invest.* **131**, (2021).

7. Hetemäki, I. *et al.* Patients with autoimmune polyendocrine syndrome type 1 have an increased susceptibility to severe herpesvirus infections. *Clin. Immunol.* **231**, 108851 (2021).

8. Bastard, P. *et al.* Auto-antibodies to type I IFNs can underlie adverse reactions to yellow fever live attenuated vaccine. *J. Exp. Med.* **218**, (2021).

9. Ferré, E. M. N. *et al.* Lymphocyte-driven regional immunopathology in pneumonitis caused by impaired central immune tolerance. *Sci. Transl. Med.* **11**, (2019).

10. Abers, M. S. *et al.* Neutralizing type-I interferon autoantibodies are associated with delayed viral clearance and intensive care unit admission in patients with COVID-19. *Immunol. Cell Biol.* **99**, 917–921 (2021).

11. Dougan, M. *et al.* Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19. *N. Engl. J. Med.* (2021) doi:10.1056/NEJMoa2102685.

12. O'Brien, M. P. *et al.* Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. *N. Engl. J. Med.* **385**, 1184–1195 (2021).

13. Vazquez, S. E. *et al.* Identification of novel, clinically correlated autoantigens in the monogenic autoimmune syndrome APS1 by proteome-wide PhIP-Seq. Elife 9, (2020).

14. Ferre, E. M. N. *et al.* Redefined clinical features and diagnostic criteria in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *JCI Insight* **1**, (2016).

15. Hedstrand, H. *et al.* The transcription factors SOX9 and SOX10 are vitiligo autoantigens in autoimmune polyendocrine syndrome type I. *J. Biol. Chem.* **276**, 35390–35395 (2001).

16. Winqvist, O., Gustafsson, J., Rorsman, F., Karlsson, F. A. & Kämpe, O. Two differentcytochrome P450 enzymes are the adrenal antigens in autoimmune polyendocrine syndrome type I and Addison's disease. *J. Clin. Invest.* **92**, 2377–2385 (1993).

17. Ishida, Y., Agata, Y., Shibahara, K. & Honjo, T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *The EMBO Journal* vol. 11 3887–3895 (1992).

18. Leach, D. R., Krummel, M. F. & Allison, J. P. Enhancement of Antitumor Immunity byCTLA-4 Blockade. *Science* vol. 271 1734–1736 (1996).

19. Hodi, F. S. *et al.* Improved survival with ipilimumab in patients with metastatic melanoma. *N. Engl. J. Med.* **363**, 711–723 (2010).

20. Failla, C. M., Carbone, M. L., Fortes, C., Pagnanelli, G. & D'Atri, S. Melanoma and Vitiligo: In Good Company. *Int. J. Mol. Sci.* **20**, (2019).

21. Husebye, E. S., Perheentupa, J., Rautemaa, R. & Kämpe, O. Clinical manifestations andmanagement of patients with autoimmune polyendocrine syndrome type I. *J. Intern. Med.* **265**, 514–529 (2009).

22. Zhu, M.-L., Nagavalli, A. & Su, M. A. Aire deficiency promotes TRP-1-specific immunerejection of melanoma. *Cancer Res.* **73**, 2104–2116 (2013).

23. Ramirez-Garcia, A. *et al.* Candida albicans and cancer: Can this yeast induce cancer development or progression? *Crit. Rev. Microbiol.* **42**, 181–193 (2016).

24. Balkwill, F. & Mantovani, A. Inflammation and cancer: back to Virchow? *Lancet* **357**, 539–545 (2001).

25. Bruserud, Ø. *et al.* A Longitudinal Follow-up of Autoimmune Polyendocrine Syndrome Type 1. *J. Clin. Endocrinol. Metab.* **101**, 2975–2983 (2016).

26. Bruserud, Ø. *et al.* Oral Tongue Malignancies in Autoimmune Polyendocrine Syndrome Type 1. *Front. Endocrinol.* **9**, 463 (2018).